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Exposure of U.S. Army personnel to strenuous physical stress under harsh environments is often a necessary circumstance to accomplish a military mission. Such exposure can significantly contribute to the casualty rate. To reduce casualties, physiological markers are required to characterize training programs relative to their capacity to impart resistance to the lethal effects of stress. The reticuloendothelial system (RES) is known to influence survival following injuries associated with shock due to significant blood loss and/or tissue damage (TD), both of which are possible consequences of combat. Studies in research animals have demonstrated elevated RES clearance function imparts reductions in heat shock mortality. Moreover, a circulating blood constituent, plasma fibronectin (PF) that mediates RES clearance, when elevated correlates with enhanced heat shock survival. In humans, physical exertion repeated over a number of days or weeks in a warm environment induces heat acclimation (HA) and significantly increases PF, while passive exposure to seasonal change fails to impart HA or elevations in PF. Together, these findings suggest PF elevation, a marker for improved RES fitness equates to an enhanced capacity to manage the lethal effects of heat stress. Fully defining the factors contributing to PF elevation is necessary to the design of training programs that improve RES fitness. Generally, PF elevation results from physical stress that imparts TD. However, the manner and severity of TD that leads to PF normalization at a higher level is not fully understood. The present study examined the influence of a single-bout (<20 min) of eccentric exercise (EE) on TD and PF level. In men and women, such exercise induced significant elevations in TD, however over 7 days post EE no consistent picture of PF elevation was recorded. Thus, rather than a single-bout of exercise resulting in significant TD, normalization of PF at a higher level may require repeated bouts of exercise inducing less severe TD.

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INFLUENCE OF A SINGLE-BOUT OF MUSCLE DAMAGING ECCENTRIC EXERCISE ON HUMAN PLASMA FIBRONECTIN LEVEL

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BACKGROUND

Known as the reticuloendothelial system (RES), the lung, liver and spleen, as well as the endothelium act as a phagocytic network to cleanse the blood stream of debris that might impair blood vessel patency and thus, circulation. As such, RES function influences survival following trauma and/or vascular shock (1,2,6,7,9-12,17,18,25,28,30) that results in significant tissue damage (TD). This suggests markers reflecting RES fitness status can assess the capacity to survive severe physiological stress, including heat stress survival. RES blood clearance rate positively correlates with rat heat stress survival (9). In addition, elevated plasma fibronectin (PF), the non-specific opsonin that mediates RES blood clearance supports reductions in rat heat stress mortality (10). Interestingly, when humans perform high-intensity physical training throughout the summer season or improve their heat acclimation (HA) by repeated physical stress in a hot environment over 7 days, PF is ultimately normalized to a higher level (6). This association between HA and PF elevation is supported by the absence of PF elevation seen with a passive response to seasonal change in which human physiological adaptation factors improve, but HA is not achieved (7). Since physical stress resulting in TD generally leads to PF elevation and thus, improved RES fitness, it is possible RES fitness might be influenced by the TD associated with intense, short-duration, physical activities that lack the capacity to affect HA. Study of such forms of exercise may provide insight into the factors supporting a HA/RES fitness correlation. Identification of these factors is required to craft training programs that enhance not only a soldier's HA capacity, but also the ability to survive a severe physiological challenge. As such, the present study examined the influence of a single-bout of eccentric exercise (EE) on TD and PF level.

ACKNOWLEDGMENTS

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EXECUTIVE SUMMARY

Exposure of U.S. Army personnel to strenuous physical stress under harsh environments is often a necessary circumstance to accomplish a military mission. Such exposure can significantly contribute to the casualty rate. To reduce casualties, physiological markers are required to characterize training programs relative to their capacity to impart resistance to the lethal effects of stress. The RES is known to influence survival following injuries associated with shock due to significant blood loss and/or TD, both of which are possible consequences of combat. Studies in research animals have demonstrated elevated RES clearance function imparts reductions in heat shock mortality. Moreover, a circulating blood constituent, PF that mediates RES clearance, when elevated correlates with enhanced heat shock survival. In humans, physical exertion repeated over a number of days or weeks in a warm environment induces HA and significantly increases PF, while passive exposure to seasonal change fails to impart HA or elevations in PF. Together, these findings suggest PF elevation, a marker for improved RES fitness equates to an enhanced capacity to manage the lethal effects of heat stress. Fully defining the factors contributing to PF elevation is necessary to the design of training programs that improve RES fitness. Generally, PF elevation results from physical stress that imparts TD. However, the manner and severity of TD that leads to PF normalization at a higher level is not fully understood. The present study examined the influence of a single-bout ($\leq$20 min) of EE on TD and PF level. In men (M) and women (W), such exercise induced significant elevations in TD, however over 7 days post EE no consistent picture of PF elevation was recorded. Thus, rather than a single-bout of exercise resulting in significant TD, normalization of PF at a higher level may require repeated bouts of exercise inducing less severe TD.

INTRODUCTION

The RES is comprised of the endothelium that forms the interior lining of all blood vessels, as well as the specialized phagocytic cells residing in the lung, liver and spleen (1). This system is known to influence survival following vascular shock and/or TD induced by hemorrhage (11,12,17,30), endotoxin (12,25,28,30), epinephrine (17), trauma (2,30), acceleration (25), tourniquet occlusion (28) and heat stress (9,10). Furthermore, shock susceptibility is increased by RES blockade (2,4,9,12,28,30). As such, the RES is hypothesized to be a common pathway for both the pathogenesis of and host resistance to shock (11,30). In part, this contribution to shock and/or TD survival is mediated by RES phagocytic clearance of particulate debris to sustain blood vessel patency (1, 2,3,15). In this regard, Kupffer cells, the specialized phagocytic entities of the liver are responsible for the majority of particulate uptake by the RES (1,8). A blood constituent known as PF binds to the vascular debris that results from TD to support its engulfment by the phagocytic cells of the RES (3,15,19,20,21). Studies in animals (9,10) and humans (6,7) suggest PF elevation and thus, improved RES fitness has potential as a marker for an enhanced capacity to survive the lethal effects of heat stress. Characterizing the factors mediating PF's normalization at elevated levels will support design of training regimens that induce improved RES fitness. Since TD serves as a stimulus for PF elevation (16,23,26,29), a single-bout of stressful, tissue damaging EE was studied to determine if PF elevation was induced, as is the case when multiple bouts of stressful exercise are employed (6).

METHODS

The present study was an adjunct of a larger study that investigated the influence of dietary supplements on muscle damage and soreness following eccentric exercise. Briefly, a double-blinded, placebo-controlled design was employed in this larger study. Forty-volunteers consumed either one placebo- or antioxidant (400mg vitamin C and 800 mg vitamin E)-supplemented sports bar 28 d before and 7 d following a single bout of EE. Biochemical markers, muscle performance, and muscle soreness were assessed before and at several time points out to 7 d post-EE. Of the 40 volunteers providing informed consent, 13 M and 11 W participated in the adjunct aspect that included PF testing. Characteristics of this subgroup of the volunteers are shown in Table 1.

Four weeks prior to performing EE, maximal oxygen uptake for each volunteer was determined using a discontinuous, progressive protocol that employed the cycle ergometer in the concentric mode. Eccentric cycle ergometry as conducted in this study has been previously described (14). The cycle ergometer was designed such that the leg cycling activity was directed against the pedal rotation generated by an electric motor. The volunteer performed eccentric muscle activity by resisting the motor's drive on the pedal crankshaft to cause the motor to run at a lower rpm. To provide necessary back support, the volunteer was seated in a rigid armchair that was positioned for each volunteer such that the distance from the armchair to the pedal crankshaft did not permit full extension of the knee. EE intensity was established for volunteers on the basis of their previously determined maximal oxygen uptake during concentric cycling exercise.

To assist maintenance of pedal rpm, the volunteer was provided with a meter that displayed the actual rpm.

Volunteers exercised at 100% of the intensity that resulted in maximal oxygen uptake at an ambient temperature of 23 to 25°C. They attempted to exercise for a total of 20 mins, with a 5 min rest following the first 10 mins of exercise.

Just before the start (Time 0) of and at 0.12, 1,2,24,48,72,96,120 and 168 (7 days) hrs post exercise, heparinized blood samples were collected for PF testing. Plasma samples were supplemented with aprotinin (5000 KIU/ml; Sigma, St. Louis) to reduced enzymatic protein degradation and then stored at –70°C. Serum samples were also collected and stored for the testing of the following TD indices: creatine kinase (CK), and myoglobin (Mb). PF assays employed standard enzyme-link immunosorbent assay (ELISA) technology (Chemicon Int.; Temecula, CA) and were conducted at USARIEM. Dr. Richard Tulley (Clinical Chemistry Laboratory; Pennington Biomedical Research Center, Baton Rouge, LA) performed the TD indices by immunoassays using commercially available kits (Sigma, St. Louis).

In addition to TD indices, 3 types of subjective assessment for delayed onset of muscle soreness (DOMS) were determined pre and post EE. In type 1 (T1), forcing their back to a wall, the volunteer slid into a seated configuration. With type 2 (T2), the volunteer was seated with their feet on the floor, while for type 3 (T3), the volunteer was seated with their legs held parallel to the floor. Soreness was scored employing a range of 0 for no soreness to 6 for intolerable soreness.

Analysis of variance with repeated measures was conducted to compare differences over time in the values for PF, TD indices and DOMS scores. When differences were noted, a Tukey's post hoc test was employed to identify those points post exercise that differed significantly from Time 0 values. The null hypothesis was rejected at $p<0.05$.

RESULTS

Analysis of changes in PF, TD indices and DOMS scores post EE between M and W relative to the presence or absence of prior dietary supplementation demonstrated no significant differences over time (data not shown). Therefore, these data were grouped by gender without regard to the dietary supplementation parameters.

Tables 1 and 2 show volunteer characteristics and EE physical performance indices, respectively. Expected gender-related differences in volunteer characteristics were noted. By design, the relative intensity during eccentric exercise was the same for all volunteers. As such, the $V0_2$ during EE for M and W was not significantly different.

For M vs. W, significant CK elevations post EE were noted relative to Time 0 values (Fig. 1a), with maximum elevations (841 ± 459 vs. 3042 ± 1507 U/ml) occurring at 72 vs. 96h, respectively. For M and W combined, CK values post EE remained significantly elevated throughout the 168 h test period (Fig. 1b). In both M and W, significant elevations for Mb relative to Time 0 (46±5 and 38±4 ng/ml) were recorded (Fig. 2a). Mb elevations were not as consistent as those for CK. For M vs. W, significant maximum Mb elevations (104±20 vs. 67±17 ng/ml) occurred at 2 vs. 48h, respectively. Due to reduced variability, combined values for M and W demonstrated significant maximum Mb (241±112 ng/ml) elevations relative to Time 0 (38±4 ng/ml) out to 96h post EE (Fig. 2b).

T1 subjective measures for DOMS revealed maximum significant elevations at 24 and 48 hrs for W and M, respectively (Fig. 3a). Significant elevations in DOMS scores were sustained out to 96 hrs for M and W. This DOMS pattern was similar for M and W combined (Fig. 3b). T2 and T3 DOMS scores were also significantly elevated following EE (data not shown); however, they were not as elevated as those for T1.

PF levels for M and W, pre and post EE, were not significantly different. M relative to W showed a steady state for PF values, with no significant elevations post EE (Fig. 4a). The regression line for W suggested rising PF levels over the 168 h test period. However, only sporadic, significant elevations relative to Time 0 at 24 and 120 hrs were noted. For M and W combined, PF changes also demonstrated a positive slope, but only the 120 h time point was significantly elevated compared to Time 0.

DISCUSSION

To enhance military performance, for example in a hot, humid environment, it is a goal of training to achieve a state of HA. However, even heat-acclimated soldiers, through the conduct of their duties may exceed this elevated thermoregulatory capacity and potentially fall victim to the lethal effects of heat stress. Should this occur, soldier survival will rely, not necessarily on those physiological mechanisms that impart HA, but those that support recovery from severe TD, shock and/or trauma. As such, to fully support prevention and reduction of military casualties, it is perhaps prudent to characterize training programs not only for their HA influence, but their impact on systems supporting trauma survival.

During the past half century, the RES has clearly been demonstrated to affect significantly survival following shock and/or trauma (1,2,11,12,17,18, 25,28,30), including shock induced by heat stress (9,10). Since PF mediates RES clearance function (4,19-21) to influence shock and/or trauma survival (10, 13,20,23), level of this circulating protein serves as a marker of RES fitness. As such, PF testing has previously been employed at USARIEM to characterize the effects of stressful exercise on RES fitness. Self-paced, daily running in a hot environment over 7 days results in HA and elevated PF (6). In another example, daily bouts of high intensity exercise over the summer months induces significant PF suppression during the first two months, while at program completion after 3 months, PF is significantly elevated (6). Since the high intensity running in this training occurred outdoors under warm summer conditions, HA improvements might be expected at 2 months, when PF is suppressed. These examples illustrate the importance of characterizing a training program relative to RES fitness; since it is possible an association and/or dissociation with HA might occur, depending on temporal and/or training severity factors.

Generally, TD serves as a stimulus for PF elevation. A typical response to severe physical stress is first, PF consumption at sites of TD, followed by recovery and then elevation when PF production exceeds consumption (16,24,29). Since multiple bouts of stressful exercise induce PF elevation in association with HA (6), it was of interest to determine the effect of a single bout of exercise that should induce significant TD, but lacks the potential to influence HA due to its short duration. Such a study would contribute to the knowledge base for the training conditions conducive to PF elevation and thus, improved RES fitness.

A single bout of EE lasting $\leq$20 min resulted in significant elevations in CK and Mb (Figs 1a-2b). The severity of the muscle TD with EE was revealed by the finding peak CK elevation at 96 hrs (Fig 1b) was more than 3 times higher than the peak CK elevation reported for 3 consecutive days of bicycling endurance training (27). DOMS indicated by mean scores exceeding 3.5 (Fig. 3) also suggested severe TD. However, over 7 days post EE, this TD damage did not stimulate PF elevation in M and only sporadic, significant PF increases in W were noted (Fig. 4). The sporadic nature of PF spikes may indicate repeated cycles of enhanced PF production following by its uptake at sites of injury. However, a lack of consistent PF elevation suggested TD-induced PF production was largely in balance with PF consumption by the TD healing process throughout the 7-day test period (26). Although, M and W PF values were not significantly different at Time 0 (Fig. 4a), the higher starting values in M may have contributed to the absence of sporadic, but significant PF spikes as seen in W. Significant elevations in Mb (Fig. 2b) and DOMS scores (Fig. 3) out to 96 hrs, and CK (Fig 1b) out to 168 hrs were indicative of a prolonged period of TD in which PF would have been consumed by the healing process. Perhaps PF testing beyond 7 days, when TD indices were no longer significantly elevated would have revealed a consistent picture of significant PF elevation. However, once PF levels have normalized after TD, PF synthesis declines (5) to suggest PF elevations beyond the 7-day test period would not be realized.

In contrast to these findings are those of a 7-day program in which multiple bouts of exercise in a hot environment led to HA and significant elevations in PF (6). The nature of this program which was self-paced with intermittent rest periods would likely result in less severe TD. Since within 7 days, PF elevation was not induced after a single-bout of tissue damaging EE, PF elevations may benefit from multiple bouts of stressful exercise that induce less severe TD. Thus, it may be the nature of multiple exposures to mild TD that is essential to the normalization of PF at a higher concentration.

CONCLUSIONS

A single bout of severe, tissue-damaging exercise was not associated with a consistent picture of PF elevation over 7 days post exercise. As such, multiple bouts of exercise with less severe tissue damage may be the key to the stimulation of PF production such that it exceeds consumption by the tissue healing process to allow PF normalization at a higher circulating concentration. This perhaps explains improved RES fitness thru PF elevation in HA programs involving repeated bouts of self-paced exercise in a warm environment conducted over a 7-day period (6).

RECOMMENDATIONS

Soldier training that results in not only improved physical conditioning, but also an elevation in PF should enhance their capacity to survive the potentially lethal effects of injuries associated with TD and/or blood loss. Normalization of PF at a higher circulating concentration is achieved following recovery from stress-induced TD. However, the stress employed should not be so severe as to cause PF consumption by the TD to delay or prevent PF elevation. Rather than a single bout of severe stress, repeated exposure to mild stress-inducing TD is recommended to stimulate a rise in circulating PF.

Figure 1a. Comparison of Creatine Kinase Levels in Men and Women, Pre and Post Eccentric Exercise. Values are means ± S.E.

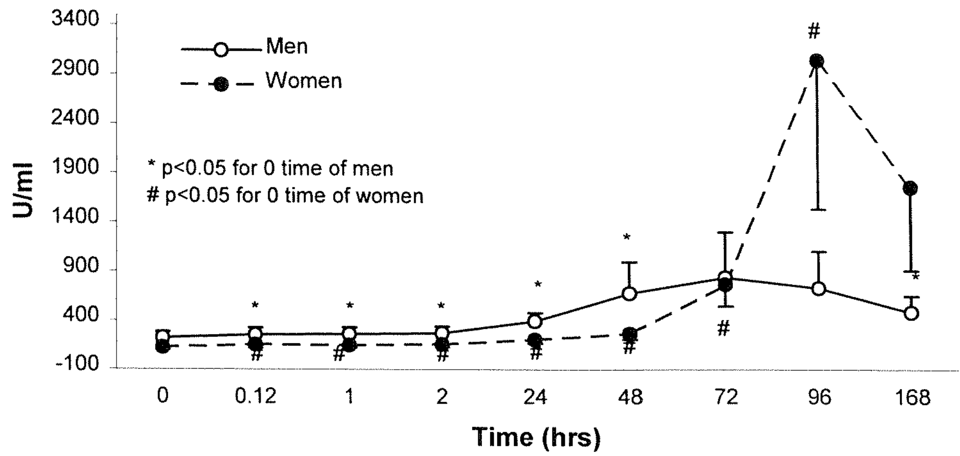

Figure 1b. Creatine Kinase Levels Pre and Post Eccentric Exercise for Men and Women Combined. Values are means ± S.E.

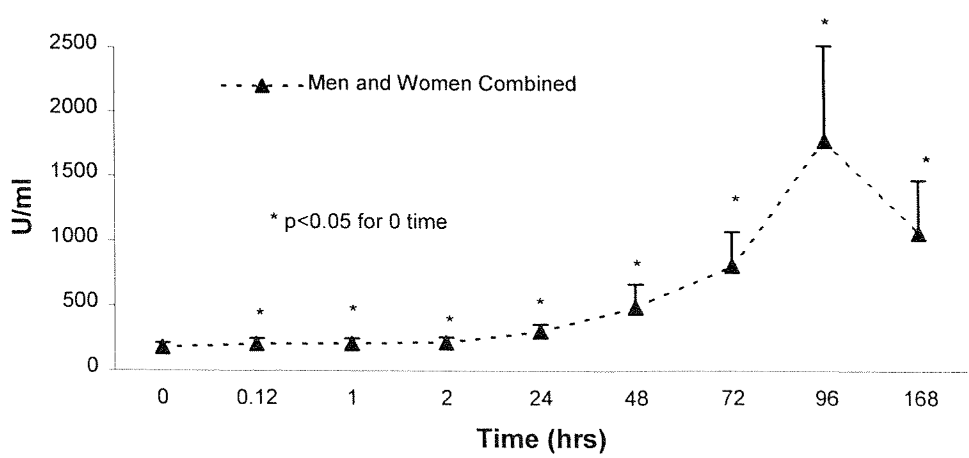

Figure 2a. Comparison of Myoglobin Levels in Men and Women, Pre and Post Eccentric Exercise. Values are means ± S.E.

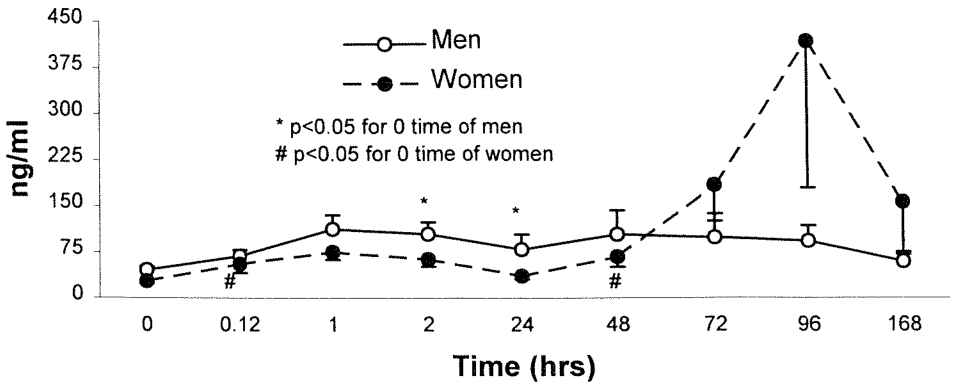

Figure 2b. Myoglobin Levels Pre and Post Eccentric Exercise for Men and Women Combined. Values are means ± S.E.

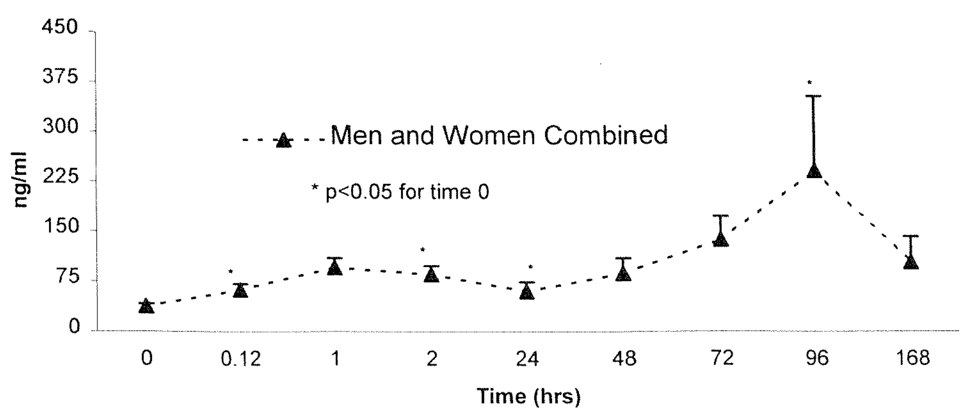

Figure 3a. Comparison of Delayed Onset of Muscle Soreness (DOMS) in Men and Women, Pre and Post Eccentric Exercise. Volunteers slid into a seated configuration with their backs forced against a wall. Soreness was scored employing a range of 0 for no soreness to 6 for intolerable soreness. Values are means ± S.E.

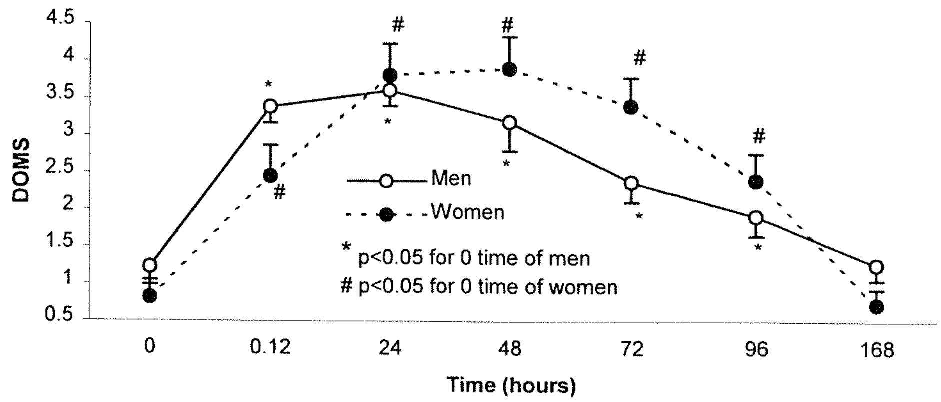

Figure 3a. Delayed Onset of Muscle Soreness (DOMS) Pre and Post Eccentric Exercise for Men and Women Combined. Volunteers slid into a seated configuration with their backs forced against a wall. Soreness was scored employing a range of 0 for no soreness to 6 for intolerable soreness. Values are means ± S.E.

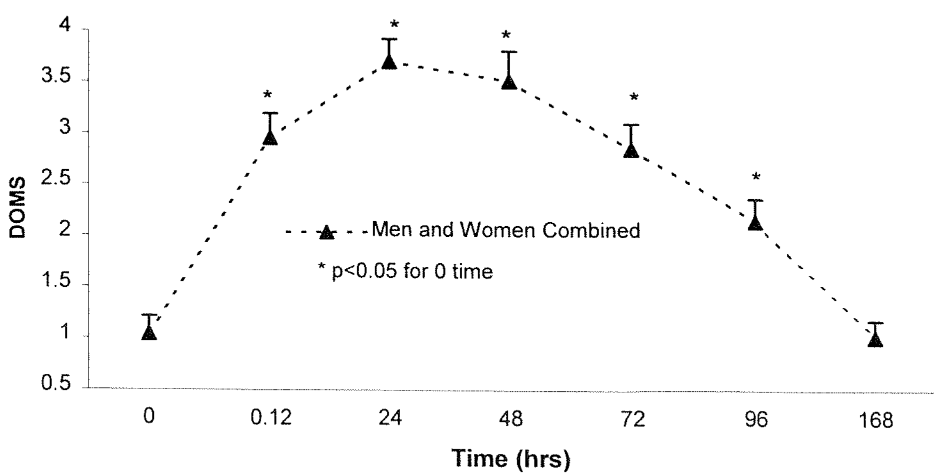

Figure 4a. Comparison of Plasma Fibronectin Level in Men and Women, Pre and Post Eccentric Exercise. Values are means ± S.E.

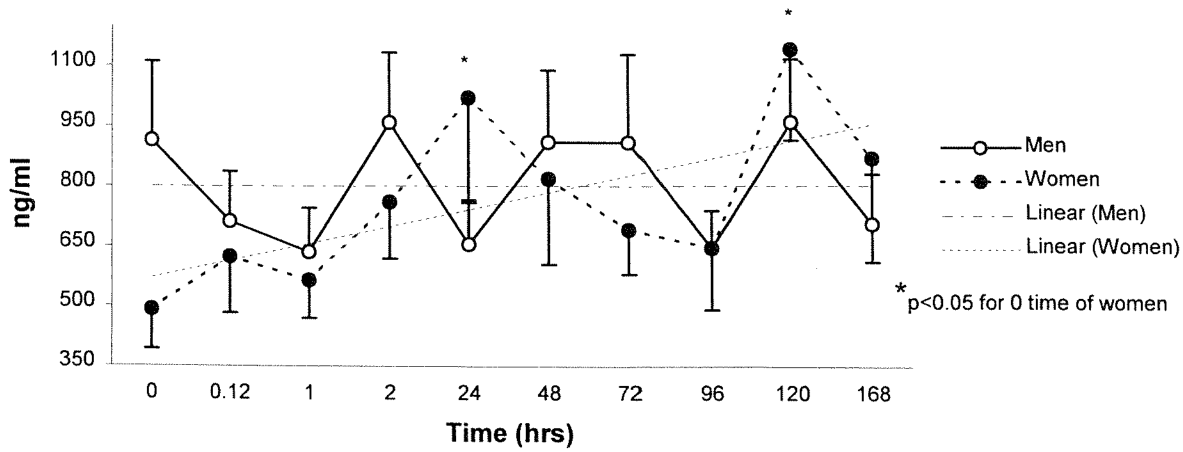

Figure 4b. Plasma Fibronectin Levels Pre and Post Eccentric Exercise for Men and Women Combined. Values are means ± S.E.

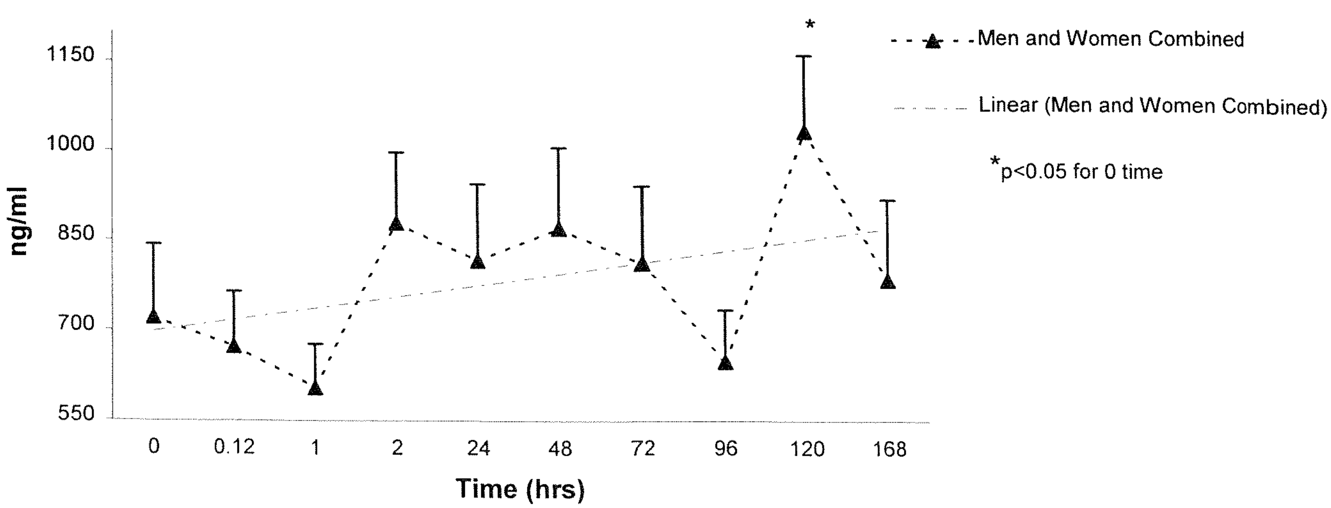

Table 1. Volunteer Characteristics

	Men	Women
Age (y)	25.4±1.6	23.0±1.5
Height (cm)	177.4±1.7	158.7±2.7*
Weight (kg)	84.6±3.5	61.0±3.1*
VO_{2max} (L/min)	3.5±0.1	2.2±0.1*

* = significantly different ($p<0.05$)

Table 2. Volunteer Physical Performance Indices with Eccentric Exercise

	Men	Women
Work Load (Watts)	297.3±8.1	174.1±7.6*
Heart Rate (bpm)	144.5±4.7	153.2±6.2
VO_2 (ml/kg/min)	21.7±1.3	20.6±1.7
% VO_{2max} (%)	52.2±2.5	55.5±4.0

* = significantly different ($p<0.05$)

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